UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,880	07/22/2003	Keith A. Webster	7230-4	1230

43463 7590 05/16/2006

RUDEN, MCCLOSKY, SMITH, SCHUSTER & RUSSELL, P.A.
222 LAKEVIEW AVE
SUITE 800
WEST PALM BEACH, FL 33401-6112

EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,880	WEBSTER, KEITH A.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/04;10/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 1 and 5, in the reply filed on 7 March 2006 is acknowledged. The traversal is on the ground(s) that the subject matter of all groups describe methods for the common goal of blocking the cell death promoting actions of the BNIP3 gene product, and target the same death pathway at different points. Accordingly, applicants assert that the search for any one group would most likely be sufficient for other groups and would therefore not constitute an undue burden. This is not found persuasive because the fact that applicant can conceive of a general commonality present between all Groups is not evidence that the searches are not divergent. Since each Group requires the use of a different BNIP3 inhibitor, each of which retains its own individual mechanism of action towards inhibiting BNIP3 activity, and each of which must be separately searched as applicants have claimed them separately, there is significant divergence in the searches between the various groups due to said different inhibitors. Accordingly, a serious burden exists to search and examine each claimed invention in a single application. However, claims 9 and 10 are re-joined, since the elected invention does not specify a cell-type, and since claims 9 and 10 are broadly embraced within the elected Group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2-4, and 6-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7 March 2006.

Information Disclosure Statement

The information disclosure statements (IDS's) submitted on 1 March 2004 and 25 October 2004 were filed before the mailing date of the instant first action on the merits. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and signed and initialed copies are enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 9, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing BNIP3 expression in cells in vitro, does not reasonably provide enablement for methods for preventing or reducing hypoxia acidosis comprising reducing BNIP3 expression or activity in cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims of the instant invention are drawn to a method for preventing or reducing hypoxia acidosis induced injury to a cell, comprising reducing BNIP3 expression or activity in the cell, wherein said reducing is accomplished via a mutant BNIP3 protein in the cell, or

wherein said cell is a myocyte, which may be a cardiomyocyte. The claimed invention embraces both *in vitro* and *in vivo* reduction of BNIP3 activity.

The claimed invention is considered to fail the enablement requirement in two regards. First, neither the specification nor the prior art are considered to provide adequate support for preventing hypoxia acidosis induced injury to a cell. The prior art is silent in regards to exemplifying prevention of such injury, and the specification provides no examples of preventing hypoxia acidosis induced injury in any cell.

The second issue which is considered to be non-enabled based upon either of the prior art or the specification is the scope of the claims drawn to *in vivo* reduction of hypoxia acidosis induced injury comprising reducing BNIP3 expression or activity in a cell, particularly in regards to the reduction of BNIP3 via the expression of a mutant BNIP3 protein in a cell.

In order to express a mutant BNIP3 protein in the cell, a mutant BNIP3 vector would first have to be transfected into the target cells of interest, utilizing gene therapy techniques. The state of the art is exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, who describes that major considerations for any gene transfer or any DNA therapy protocol must include:

1) the type of vector and amount of DNA constructs to be administered,

2) the route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) how much of the expressed proteins are needed to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, such methods would have to be altered for the treatment of each disease based on the specific vector used, the route of administration, the animal being treated, and therapeutically effective amount of the DNA.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, whether the claimed method can generate a therapeutic effect, or, without resorting to undue experimentation, how one of skill would practice the nucleic acid therapy method as recited in the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the invention in vitro. Given that gene therapy to correct a disease or a medical condition in any animal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector, one skilled in the art would have to resort to an undue quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9, and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Kubasiak et al. (Kubasiak L. et al. ,Circulation (23 OCT 2001) Vol. 104, No. 17, Supp. [S], pp. 203-203).

The claims of the instant invention are drawn to a method for preventing or reducing hypoxia acidosis induced injury to a cell, comprising reducing BNIP3 expression or activity in the cell, wherein said cell is a myocyte, which may be a cardiomyocyte.

Kubasiak et al. teaches a method for reducing hypoxia acidosis induced injury to a cell, comprising reducing BNIP3 expression or activity in the cell, wherein said cell is a cardiomyocyte.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Vande Velde et al. (Mol. Cell. Biol. 2000. 20(15) 5454-5468).

The invention of the above claims is drawn to a method for preventing or reducing hypoxia acidosis induced injury to a cell, comprising reducing BNIP3 expression or activity in the cell, wherein said reducing is accomplished via the expression of a mutant BNIP3 protein in the cell.

Vande Velde et al. teaches a method comprising reducing BNIP3 expression or activity in the cell, wherein said reducing is accomplished via the expression of a mutant BNIP3 protein in the cell. Although Vende Velde et al. is silent as to the effect of such administration on preventing or reducing hypoxia-acidosis induced injury of a cell, Vande Velde et al. nevertheless teaches all the active steps of the instant claims. Accordingly, since the prior art teaches all the structural and manipulative steps as those instantly claimed, the effect of preventing or reducing hypoxia acidosis induced injury to a cell is considered to be an inherent result of the expressing a mutant BNIP3 protein in a cell.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vande Velde et al. as applied to claims 1 and 5 above, and further in view of Bruick (Proc. Natl. Acad. Sci USA 2000 97(16) 9082-9087.

The claims of the instant invention are drawn to a method for preventing or reducing hypoxia acidosis induced injury to a cell, comprising reducing BNIP3 expression or activity in the cell, wherein said reducing is accomplished via the expression of a mutant BNIP3 protein in the cell, or wherein said cell is a myocyte, which may be a cardiomyocyte.

Vande Velde et al. teaches a method comprising reducing BNIP3 expression or activity in the cell, wherein said reducing is accomplished via the expression of a mutant BNIP3 protein in the cell. Although Vende Velde et al. is silent as to the effect of such administration on preventing or reducing hypoxia-acidosis induced injury of a cell, Vande Velde et al. nevertheless teaches all the active steps of the instant claims. Accordingly, since the prior art teaches all the structural and manipulative steps as those instantly claimed, the effect of preventing or reducing hypoxia acidosis induced injury to a cell is considered to be an inherent result of the expressing a mutant BNIP3 protein in a cell.

Vande Velde et al. does not teach the expression of a mutant BNIP3 protein in myocytes or cardiomyocytes.

Bruick teaches that BNIP3 (Nip3 of Bruick) is highly expressed in response to hypoxia, and that hypoxia-induced apoptosis plays an important role in the pathology of many diseases including ischemic damage to the heart and cardiomyocytes in particular. Bruick also hypothesizes that BNIP3 plays a direct role in the progression of hypoxia-mediated apoptosis in myocardial ischemia.

It would have been obvious to one of ordinary skill in the art to use the method of reducing BNIP3 activity by expressing a mutant BNIP3 protein in cells as taught by Vande Velde et al. in cardiomyocytes.

One of ordinary skill in the art would have been motivated to practice the method of Vande Velde in cardiomyocytes because Bruick et al. hypothesize is that BNIP3 plays a direct role in the progression of hypoxia mediated apoptosis in myocardial ischemia. One would of been motivated to inhibit BNIP3 activity in myocardial cells for the purpose of investigating the role that BNIP3 plays in hypoxia mediated apoptosis, since such events underlie myocardial infarction.

One of ordinary skill would of had a reasonable expectation of success, since expression of the mutant BNIP3 protein is expressly taught by Vande Velde et al., and since the only difference would merely be to practice such methods in different cell types, i.e. cardiomyocytes. Accordingly, the invention would have been considered prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER